REMARKS

The following remarks are in response to the Examiner's Office Action mailed on March 14, 2006. Claims 74-83 have been canceled. Claims 1, 12, 34, 40, 46, and 48 have been amended. Claims 1-73 are now pending. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

I. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 40-47 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite in that the preamble of the method and the final step do not agree. Applicants amend independent claims 40 and 46 to render the final step consistent with the preamble of the method claimed. Withdrawal of the rejection is therefore respectfully requested.

II. Rejection under 35 U.S.C. § 103(a)

1. Over Yang et al. and Fishel et al.

Claims 1-22, 24-33, 36, 38-39, 42, 44-45, 49-58, 60-63 and 65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yang et al. (PG Publication 2002/0042061) in view of Fishel et al. (U.S. Patent No. 6,333,153). Applicants respectfully traverse the Examiner's rejection based on the following reasons.

The claimed invention is directed toward a method for detecting nucleotide sequence variation of a target nucleic acid relative to that of a reference nucleic acid, such as a single nucleotide polymorphism (SNP). By exploiting the three-way molecular interactions of a Holliday junction (HJ) structure (e.g., formed by a target nucleic acid containing a SNP and a reference nucleic acid), an HJ-binder (e.g., RuvA), and a receptor for the HJ-binder (e.g., an antibody against RuvA) which is immobilized to a substrate, the difference between the target nucleic acid and the reference nucleic acid is efficiently detected.

In contrast, none of the references cited teaches or suggests such an approach for detecting nucleic acid differences. As acknowledged by the Examiner, Yang et al. does not specifically teach a method wherein the complex formed by an HJ structure and an HJ-binder is

contacted with a receptor. Nowhere does Yang et al. teach detecting nucleic acid differences based on the three-way interactions between an HJ structure, an HJ-binder, and a receptor for the HJ-binder. Yang et al. merely mentioned in passing that an ELISA assay may be used for detecting the binding of a Holliday junction binding protein to a Holliday junction. Paragraph 0102. However, Yang et al. does not teach or suggest how the differences between a target nucleic acid and a reference nucleic acid can be detected by an ELISA.

The secondary reference cited, Fishel et al., fails to fill in the gap between the teaching of Yang et al. and the claimed invention. In fact, Fishel et al. teaches away from the claimed invention. Specifically, Fishel et al. discloses compositions and methods for binding MutS homologs (e.g., MSH dimers) to mismatched DNA in the presence of ADP. *See* Abstract. Fishel et al. pointed out that "if the dimer is used in the form of a mismatched duplex DNA-containing liquid then it may be necessary to dissociate, and possibly to separate, the dimer from the mismatched DNA prior to using it in the composition, kits, and methods of the invention." Column 21, lines 18-27. Nowhere does this reference teach the claimed method involving the steps of

> contacting the first complex with a receptor for the Holliday junction-binder that specifically recognizes the Holliday junction-binder and is immobilized to a substrate;
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> forming a second complex between the first complex and the receptor for the Holliday junction-binder; and
>
> detecting the presence of the Holliday junction structure in the second complex, wherein the presence of the Holliday junction structure in the second complex is indicative of the sequence difference between the target nucleic acid and the reference nucleic acid.

In determining the scope and content of the prior art, references must be considered in their entirety, as a whole, including portions that would lead away from the claimed invention. *In re Panduit*, 810 F.2d 1561, 1 U.S.P.Q. 2d 1593 (Fed. Cir. 1987). Hindsight reconstruction using the disclosure and claims in prosecution as a guide to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention is not permitted. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). References must be evaluated by ascertaining the facts fairly disclosed therein as a whole. It is impermissible to first ascertain factually what Applicants have done and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct Applicants'

invention from such prior art. The references viewed by themselves and not in retrospect must suggest what an applicant has done. *In re Schaffer,* 229.F.2d 476, 108 U.S.P.Q. 326 (1956) and *in re Skoll*, 523 F.2d 1392, 187 U.S.P.Q.1981 (CCPA 1975). The mere fact that it is possible for two isolated disclosures to be combined does not render the result of that combination obvious absent a logical reason of record, which justifies combination. *In re Regel*, 626 F.2d 1399, 188 U.S.P.Q. 136 (CCPA).

The merely mentioning of ELISA in Yang et al. and the teaching away of Fishel et al. do not give a clue to one of ordinary skill in the art as to how to detect nucleic acid differences based on the three-way interactions between an HJ structure, an HJ-binder, and a receptor for the HJ-binder. Absent objective evidence to the contrary, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of these grounds of rejection is therefore respectfully requested.

2. Over Yang et al., Fishel et al. and Lishanski

Claims 34-35, 40-41, 46-48, 64, 68-71, and 73 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Yang et al. in view of Fishel et al. and further in view of Lishanski (U.S. Patent No. 6,013,439). Applicants respectfully traverse the Examiner's rejection based on the following reasons.

As discussed in detail above, neither Yang et al. nor Fishel et al, each alone or in combination, teaches or suggests a method of detecting nucleic acid differences based on the three-way interactions between an HJ structure, an HJ-binder, and a receptor for the HJ-binder. Lishanski also fails to fill in the gap between the two cited references and the claimed invention. In contrast, Lishanski discloses labeling the wildtype and mutant homoduplex with different detectable labels (such as biotin and digoxin) to allow detection of the formation of HJ structure based on association of the two labels. *See* Example 1, step 6, column 39, lines 36-48.

In view of the failure of the cited references to teach or suggest the claimed invention, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of these grounds of rejection is therefore respectfully requested.

3. Over Yang et al., Fishel et al., Lishanski and D' Elia et al.

Claim 72 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Yang et al. in view of Fishel et al. and further in view of Lishanski and D' Elia et al. (PG Publication 2002/0039761). Applicants respectfully traverse the Examiner's rejection based on the following reasons.

As discussed in detail above, none of Yang et al., Fishel et al, and Lishanski teaches or suggests a method of detecting nucleic acid differences based on the three-way interactions between an HJ structure, an HJ-binder, and a receptor for the HJ-binder. D' Elia also fails to fill in the gap between the three cited references and the claimed invention. D' Elia merely discloses the use of His-tags fused with proteins. Paragraph 0031. Nowhere does this reference teach or suggest the claimed method.

In view of the failure of the cited references to teach or suggest the claimed invention, a prima facie case of obviousness has not been established under 35 U.S.C. §103(a). Withdrawal of these grounds of rejection is therefore respectfully requested.

CONCLUSION

In view of the above amendments and remarks, Applicants earnestly believe that the pending claims are in condition for allowance and respectfully request the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any question, the Examiner is encouraged to telephone the undersigned.

The Commissioner is authorized to charge any additional fees that may be required, including petition fees and extension of time fees, or credit any overpayment to Deposit Account No. 23-2415 (Docket No. 26757-717.201).

Respectfully submitted,

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